Remarks

Claims 1-3, 7, and 16-21 were pending prior to this Response. By the present communication, no claims have been added or canceled, and claims 1 and 17 have been amended to define Applicants' invention with greater particularity. Support for the amended claims may be found, among others, at page 15, lines 8-19, of the specification as filed. The amendments do not raise any issues of new matter and the amended claims do not present new issues requiring further consideration or search. Accordingly, upon entry of the present amendment, claims 1-3, 7, and 16-21 will be pending in this application.

Rejection under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1-3, 7, 16-18, 20, and 21 under 35 U.S.C. §103(a) as allegedly unpatentable over Giuliani, *et al.* J. Exp. Med. April 1998, Vol. 187, No. 7, 1123-1132 (hereinafter "Giuliani") in view of Esposito, *et al.* Infection and Immunity, July 1970, Vol. 2, No. 1, 120-22 (hereinafter, "Esposito"). In addition, Applicants respectfully traverse the rejection of claims 1-3, 7, 16, 17, and 19-21 as allegedly unpatentable over Esposito.

The recent U.S. Supreme Court decision in the *KSR International v. Teleflex Inc.* (82 USPQ2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the *KSR* rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

The Office Action alleges that Giuliani teaches LTR72, a mutant where one or more amino acid residues are substituted, inserted, deleted, or added, and having adjuvant activity, while the existing serine, glutamic acid and lysine residues are retained. However, Giuliani notes that LTR72 still has a low residual level of toxicity. The Office Action relies upon Esposito for teaching a composition comprising attenuated cholera toxin, which is made by

detoxification using formalin at a temperature of 35°. As such, the Office Action concludes that one of skill in the art would have been motivated to further attenuate LTR72 with formalin at a temperature of 35°, as set forth in Esposito.

Applicants respectfully disagree with the Examiner's position because there has been no motivation for one ordinary skilled in the art to combine teachings of Giuliani and Esposito. As discussed in the response filed on January 23, 2006, Esposito seems to have utilized "*crude*" cholera toxin to produce a toxoid, and thus their toxoid would have comprised proteins or other components in addition to the cholera toxin protein. Cholera-toxin-producing bacteria produce not only cholera toxin protein but also a protein called "endotoxin" on their cell surface, and this endotoxin is known to possess adjuvant activity. Therefore, even if Esposito's formalin-treated *crude* cholera toxin had an adjuvant activity (in reality, Esposito only describes the *antigenicity* of formalin treated *crude* cholera toxin and fails to teach or suggest its *adjuvant activity*), there remains a possibility that Esposito's *crude* cholera toxin included endotoxin or other proteins and these materials were the true origin of the adjuvant activity.

Applicants submit that from the Esposito's teaching, it is unknown as to what protein in their *crude* cholera toxin (a mixture of cholera toxin and various other protein components) actually has an antigenicity or adjuvant activity. Furthermore, formalin treatment on *crude* cholera toxin may cause formation of a complex of proteins including a cholera toxin protein, and thus, even if one skilled in the art attempts to purify a cholera toxin or other material having antigenicity or adjuvant activity in the formalin-treated *crude* toxin of Esposito, there is no guarantee of obtaining a material that is identical to the claimed adjuvant.

The structure of a complex that may be formed with cholera toxin and other proteins would be much more complicated than that of the cholera toxin protein. Therefore, Applicants submit that one of skill in the art would not know how to isolate and purify attenuated cholera toxin or other materials having antigenicity or adjuvant activity from the resulting complex. Moreover, as of the priority date of the present application, it has been believed that toxic activity and adjuvant activity are closely related to each other and that a high level of reduction of toxin activity does not lead to development of adjuvants with high safety, because the reduction is associated with a decrease of the immuno-enhancing activity (see pages 12-13 of the

specification). In view of this knowledge in the art, there would have been *no* motivation for one skilled in the art to treat Giuliani's mutant-type toxin with formalin for further detoxification, since the skilled person would have expected that such detoxification would cause loss of adjuvant activity.

Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claim 1 to limit the toxins used to produce the adjuvant. By this amendment, an adjuvant produced by purifying and attenuating a "natural cholera toxin" and a mutant "heat-labile toxin of pathogenic *E. coli*" have been removed from the claimed scope; thus it has been further clarified that Giuliani and/or Esposito do not disclose each and every claim limitation. As discussed above, a high level of detoxification and the maintenance of adjuvant activity are two conflicting objectives and it was common knowledge in the art at the time of the priority date of the instant application that a high level of reduction in toxicity would lead to disappearance of adjuvant activity. Contrary to this common technical knowledge, the present inventors successfully provided highly attenuated toxins while retaining adjuvant activity. Thus, since Applicants identified the unexpected result of producing a highly attenuated toxins while retaining adjuvant activity, Applicants submit that a *prima facie* case of obviousness has not been established. Withdrawal of the rejection is respectfully requested.

Conclusion

In summary, for the reasons set forth herein, Applicants maintain that the claims clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge $1,830.00 as payment for the Petition for the Three-Month Extension of Time fee ($1110.00), the Information Disclosure Statement fee ($180.00), and the Notice of Appeal fee ($540.00) to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

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